Euthyroid and primarily hypothyroid patients develop milder and significantly more asymmetrical Graves ophthalmopathy

A K Eckstein,1 C Lösch,2 D Glowacka,1 M Schott,3 K Mann,4 J Esser,1 N G Morgenthaler5

ABSTRACT

Background and aims: Retrospective, observational study to compare clinical symptoms and TSH-receptor antibodies (TRAb) in Graves ophthalmopathy (GO) in euthyroid and primarily hypothyroid patients to those in hyperthyroid patients.

Methods: Clinical symptoms (NOSPECS (severity) and CAS (activity) score), prevalence and levels of thyroid specific antibodies and the course of the disease were evaluated in 143 primarily hyperthyroid, 28 primarily euthyroid and 11 primarily hypothyroid patients with GO.

Results: Patients with euthyroid/hypothyroid GO developed significantly less severe GO symptoms (NOSPECS score 4.4 vs 5.7; p = 0.03), less active GO (CAS score 3.9 vs 5.2; p = 0.02) and more asymmetrical disease (proptosis side difference: 1.9 mm vs 1.0 mm (p = 0.01); side difference of ≥3 mm: 23% vs 4.8%) than hyperthyroid patients. TRAb levels 6 months after GO onset were significantly lower (2.2 IU/l, p = 0.02) in euthyroid/hypothyroid than in hyperthyroid patients (8.6 IU/l), as was the prevalence of both TRAb and thyroid peroxidase antibodies (75% vs 94.6%, p = 0.0008).

Conclusions: The knowledge about the phenotype of GO in primarily euthyroid and hypothyroid patients is helpful for differential diagnosis and patient consultation. TRAb titres are very low in these patients, and the availability of a sensitive assay technique is therefore an important diagnostic tool in euthyroid and hypothyroid patients.

Graves ophthalmopathy (GO) usually occurs in a close temporal relationship with hyperthyroidism. It is rare in patients with normal thyroid function (euthyroid GO) and in patients with hypothyroid forms of thyroid autoimmune disease (hypothyroid GO). The prevalence of GO in primarily euthyroid and primarily hypothyroid patients ranges between 1.6 and 8.6%.1–4

Diagnosing GO is usually straightforward, but other diagnoses have to be considered in patients with normal thyroid function and only individual signs of GO such as isolated proptosis; these include cavernous carotid fistula,3 sphenoid meningioma and other tumours and lymphoma which may all also accompany GO itself.5

Determination of thyroid-specific antibodies contributes to the diagnosis of underlying thyroid disease. Kho et al found positive results for thyroid-stimulating immunoglobulin (TSI; 95.8%), a first-generation porcine TSH-binding inhibitory immunoglobulin (pTBII; 18.8%) and a second-generation human TSH-binding inhibitory immunoglobulin (hTBII; 81.3%) in 19 euthyroid patients among 1020 with GO. TRAb were detectable by at least one method in all patients.2 One-quarter of euthyroid patients develop thyroid dysfunction in the later course of the disease.2

The objectives of this study were to compare clinical symptoms in primarily euthyroid and primarily hypothyroid patients with those in patients with hyperthyroid GO, and to investigate the levels of thyroid-specific antibodies in these patients.

PATIENTS AND METHODS

Ethics
The study was approved by the Medical Ethics Committee of the University Essen, Germany. Written consent to be included in the database and to draw blood was obtained from all participants.

Study design
This was a retrospective observational study on data selected from a GO database started in 2000 which includes findings in 893 consecutive patients treated at the University Hospital of Essen, Germany.

Inclusion criteria
Patients were included if they:

▶ presented within 6–12 months of onset of GO before anti-inflammatory treatment;
▶ were followed up for at least 12 months after onset of GO/until they reached inactivity;
▶ had TRAb and thyroid peroxidase (TPO) antibodies (Ab) titres available 6 months after GO onset;

Consecutive primarily hyperthyroid patients out of the years 2003 and 2004 in the registry were selected as a control group.

GROUPING OF THE PATIENTS

Hyperthyroid patients
Patients who developed clinical or subclinical hyperthyroidism (elevated/normal FT4 and suppressed TSH) before or within 6 months after the onset of GO were assigned to the hyperthyroid group.

Hypothyroid patients
Patients who developed clinical or subclinical hypothyroidism (reduced/normal FT4 and elevated
TSH levels between 0.5 and 1 mU/l.

Euthyroid patients
Patients who had TSH and FT4 values within the reference range before and within 6 months after GO onset were assigned to the euthyroid group.

Treatment
Hyperthyroidism was treated with antithyroid drug (ATD) therapy for 1 year. Hyperthyroid patients who relapsed were given radioiodine therapy, underwent thyroidectomy or had a further cycle of ATD for 1 year, according to their preference. Hypothyroid patients were substituted with i-thyroxine to TSH levels between 0.5 and 1 mU/l.

Concerning ophthalmopathy, all patients received standard anti-inflammatory treatment. During follow-up, all patients with clinical activity score (CAS) values ≥2 were offered treatment with steroids. For mild and moderate disease, they received an oral regime beginning with about 1.5 mg fluoroocortolone/mg body weight. Most of the patients received 100 mg as the starting dosage. Patients with a lower body weight started with 8 days of 90 mg or 12 days of 80 mg or 16 days of 70 mg per day (according to the weight). Afterwards, the dosage was tapered by 10 mg every 4 days. The treatment was finished with 4 days of 5 mg. Thus, the whole treatment duration was 44 days (cumulative dosage when starting with 100 mg/day was 2.22 g). For severe disease (increase/duration was 44 days (cumulative dosage when starting with the dosage was tapered by 10 mg every 4 days. The treatment with steroids. For mild and moderate disease, they received an oral regime beginning with about 1.5 mg fluoroocortolone/mg body weight. Most of the patients received 100 mg as the starting dosage. Patients with a lower body weight started with 8 days of 90 mg or 12 days of 80 mg or 16 days of 70 mg per day (according to the weight). Afterwards, the dosage was tapered by 10 mg every 4 days. The treatment was finished with 4 days of 5 mg. Thus, the whole treatment duration was 44 days (cumulative dosage when starting with 100 mg/day was 2.22 g). For severe disease (increase/duration was 44 days (cumulative dosage when starting with the dosage was tapered by 10 mg every 4 days. The treatment with steroids. For mild and moderate disease, they received an oral regime beginning with about 1.5 mg fluoroocortolone/mg body weight. Most of the patients received 100 mg as the starting dosage. Patients with a lower body weight started with 8 days of 90 mg or 12 days of 80 mg or 16 days of 70 mg per day (according to the weight). Afterwards, the dosage was tapered by 10 mg every 4 days. The treatment was finished with 4 days of 5 mg. Thus, the whole treatment duration was 44 days (cumulative dosage when starting with 100 mg/day was 2.22 g). For severe disease (increase/duration was 44 days (cumulative dosage when starting with the dosage was tapered by 10 mg every 4 days.
Clinical science

Table 1 Patient and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hyperthyroid patients</th>
<th>Euthyroid and hypothyroid patients</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients (male/female)</td>
<td>143 (18/125)</td>
<td>39 (9/31)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years, median (range))</td>
<td>49 (21 to 79)</td>
<td>51 (33 to 84)</td>
<td>NS</td>
</tr>
<tr>
<td>Non-smoker/smoker</td>
<td>55/88</td>
<td>18/21</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up after first symptoms of GO (months, median (range))</td>
<td>36 (18 to 73)</td>
<td>27 (12 to 79)</td>
<td>NS</td>
</tr>
<tr>
<td>Thyroid volume (ml, mean (range))</td>
<td>23 (8 to 102)</td>
<td>14 (2 to 36)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>TBII levels 6 months after first symptoms of GO (IU/l, median (range))</td>
<td>8.6 (&lt;1.5 to &gt;40.0)</td>
<td>2.2 (&lt;1.5 to &gt;40)</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>Prevalence of positive TBII 6 months after first symptoms of GO (no (% of patients))</td>
<td>134 (94%)</td>
<td>27 (69%)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Prevalence of negative TBII and TPO Ab 6 months after first symptoms of GO (no (% of patients))</td>
<td>8 (5.6%)</td>
<td>10 (25%)</td>
<td>p = 0.0008</td>
</tr>
</tbody>
</table>
| TPO Ab levels 6 months after first symptoms of GO (IU/ml, median (range)) | 262 (<60 to >3000) | 100 (<60 to >3000) | NS |}

GO, Graves ophthalmopathy; SD, standard deviation; TBII, TSH-binding inhibitory immunoglobulin; TPO Ab, thyroid peroxidase antibodies.

statistically significant. Patient and disease characteristics are given in table 1.

Ophthalmological findings

Representative patient examples are given in fig 1. All three patients show the typical asymmetrical unilateral manifestation of GO in euthyroid and primarily hypothyroid patients. The diagnosis in the first patient was straightforward (fig 1A–C) because of the typical inferior rectus and levator palpebrae involvement and the soft-tissue inflammation. Although thyroid-specific antibody levels in the borderline range had been measured once, this patient had not developed thyroid abnormality after 19 months of follow-up. The patient in fig 1D–F was referred for biopsy with a suspected diagnosis of lymphoma with normal thyroid function. Closer thyroid work-up revealed positive TPOAb (168 U/ml) and TRAb in the euthyroid and hypothyroid patients had positive findings 100 IU/l in euthyroid and hypothyroid patients.

The mean thyroid volume was 13 ml (SD 7.6; range 2–36) in euthyroid and hypothyroid patients and was significantly smaller (82% vs 96%, p = 0.007) and, if soft-tissue inflammation was already present, did not worsen so severely (fig 2C). None of the euthyroid or hypothyroid patients developed optic neuropathy, while 10 (7%) primarily hyperthyroid patients did. Median monocular excursions were significantly (p = 0.04) less reduced in the euthyroid and hypothyroid GO patients (median 35°) than in the hyperthyroid patients (median 50°). The mean Hertel values were very similar in both groups, but there was a significantly higher side difference between both eyes (1.0 mm (hyperthyroid patients) vs 1.9 mm (euthyroid and hypothyroid patients); p = 0.01). Significantly more euthyroid and hypothyroid patients (23%) developed very asymmetrical GO with a proptosis difference of ≥3 mm (p = 0.004) (fig 2B).

Both patient groups received equal amounts of steroids, but irradiation was necessary in only 38% of the euthyroid and hypothyroid patients in comparison with 68% of the hyperthyroid patients (p = 0.03).

Endocrinological findings

The mean thyroid volume was 13 ml (SD 7.6; range 2–36) in euthyroid and hypothyroid patients and was significantly smaller than in hyperthyroid patients 50 ml (SD 22; range 8–102).

TRAb levels 6 months after GO onset were significantly higher in hyperthyroid patients (median: 8.6 IU/l) than in euthyroid and hypothyroid patients (median: 2.2 IU/l; p = 0.02) (fig 5). Median TPOAb levels 6 months after GO onset were not significantly different: 262 IU/l in hyperthyroid patients and 100 IU/l in euthyroid and hypothyroid patients.

Six months after the first symptoms of GO, only 27 (69%) of the euthyroid and hypothyroid patients had positive findings.
for TRAb, while findings were positive in 134 (94%) hyperthyroid patients. This difference was statistically significant ($p < 0.0001$). Regarding TRAb and TPOAb together, still 10 out of 39 (25%) euthyroid and hypothyroid patients were negative for both antibodies in comparison with only eight out of 143 (5.6%) hyperthyroid patients ($p = 0.0008$).

During the follow-up, six of the euthyroid patients (20.7%) developed hypothyroidism which was substituted with L-thyroxine. Two patients (6.8%) became hyperthyroid and received ATD. Among the hyperthyroid patients, following ATD treatment, 29 patients (20.3%) went into thyroid disease remission, while 114 patients (79.7%) needed definitive thyroid therapy (radioiodine therapy or thyroidectomy).

**DISCUSSION**

The clinical signs and symptoms of GO in primarily euthyroid and hypothyroid patients differ from those in primarily hyperthyroid patients: primarily euthyroid and hypothyroid patients show less soft-tissue involvement and more asymmetrical disease, and the clinical manifestations are less marked. Unilateral GO has often been reported in case reports of primarily euthyroid patients.13–15

The diagnosis of GO is considerably impeded by monosymptomatic and asymmetrical manifestations, especially in primarily euthyroid patients, and diagnostic imaging is indicated in all such patients.5–7 15 16

There is a close temporal relationship between the onset of hyperthyroidism and the onset of GO, but 4–18%17 18 of the patients with Graves disease develop thyroid dysfunction after the onset of GO, most within 1 year of the onset of eye symptoms. Regular thyroid function tests are therefore indicated in primarily euthyroid patients. About one-quarter of primarily euthyroid patients will develop thyroid dysfunction within 4 years. Predictors of this were shown to be suppressed

### Figure 1
Representative examples of euthyroid and hypothyroid patients. (A) Enface photograph of a 46-year-old patient with severe left unilateral GO with soft tissue inflammation, proptosis and marked impairment of motility. (B) Coronary and transverse (C) MRI scans showing thickening and inflammation, especially of the inferior rectus and levator palpebrae muscle. (D) Enface photograph of a 48-year-old patient with mild right unilateral GO with upper lid swelling and retraction, and mild dacryoadenitis, who was referred for biopsy with suspected diagnosis of lymphoma. (E, F) representative MRI scans of patient D showing mild dacryoadenitis and levator palpebrae muscle thickening and inflammation. (G) Enface photograph of a 34-year-old patient with right unilateral GO with proptosis without any other sign of GO, with suspected diagnosis of retrobulbar tumour. (H) MRI showing only and increase in retrobulbar adipose tissue. (I, K) Photographs of the left and right hand side showing the degree of proptosis.

### Figure 2
(A) Clinical symptoms of patients with Graves ophthalmopathy (GO) and primary hyperthyroidism (black) in comparison with patients with GO and euthyroid or primarily hypothyroid disease (grey). (B) Percentage of patients with a proptosis difference of $\geq 3$ mm. (C) Intensity of soft-tissue inflammation.
TSH and positive TRAb. Other minor abnormalities (uneven uptake and the presence of hot or warm lesions), which indicate thyroid involvement in primarily euthyroid patients with GO, are seen in the scintigram. 

Figure 3  TSH-receptor antibodies (TRAb) values in primarily hyperthyroid and primarily euthyroid and/hypothyroid patients 6 months after Graves ophthalmopathy onset.

Ethics approval: Ethics approval was provided by the Medical Ethics Committee of the University Essen, Germany.

Competing interests: None.

Patient consent: Obtained.

REFERENCES


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